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Spatiotemporal and demographic variation in the association between temperature variability and hospitalizations in Brazil during 2000–2015: A nationwide time-series study

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ABSTRACT

Background: Extreme temperature events are known to be adversely associated with a range of health outcomes, but little is known about the effect of less extreme, but more frequent fluctuation in temperature. We examined the spatiotemporal and demographic variation in the effect of temperature variability (TV) on nationwide hospitalizations in Brazil during 2000–2015.

Methods: Data on daily hospitalizations and weather variables were collected from 1814 cities, comprising 78.4% of Brazilian population. TV was defined as the standard deviation of daily minimum and maximum temperatures during exposure days. City-specific TV effect was estimated using a quasi-Poisson regression model, and then pooled at the national and regional level using meta-analysis. Stratified analyses were performed by sex, 10 age-groups, and 11 cause categories. Meta-regression was applied to city-year-specific estimates to examine the temporal change.

Results: The estimate of TV effect peaked on 0–1 days' exposure, contributing to 3.5% [95% confidence interval (CI): 3.1–3.8%] of hospitalizations nationwide, equalling 221 (95%CI: 200–242) cases per 100,000 population annually. The effect estimate varied across 11 cause categories, which was strongest for respiratory admissions. Males, particular those 10–49 year old were more affected than females but there was no sex difference for the attributable hospitalization rate. The attributable rate for the under-fives was twice as high as for the elderly, and five times higher than in adults. The majority of the most affected cities were located in the central west and the inland of northeast. The risk of hospitalization related to TV showed a significant increase over the 16-year period at the national level.

Conclusions: In Brazil, the effect of TV on hospitalization is acute, and varies by spatial, sex, age, and cause category. Given there is no evidence regarding TV adaptation, hospitalization burden associated with TV is likely to further increase and warrants consideration when developing future public health policies in the context of climate change.

1. Introduction

Climate change has been identified as posing the single largest threat for global health in the 21st century (Intergovernmental Panel on Climate Change, 2015). Most of the evidence regarding the relationship between temperature change and health outcomes has tended to focus on the adverse effect of extreme temperature events (e.g., heatwaves and cold spells) (Gasparrini et al., 2015; Guo et al., 2017; O'Neill and Ebi, 2009). By contrast, the influence of temperature variability (TV), representing weather instability within a few days, has been less investigated. To date, most studies have examined the mortality risk associated with either intra- (e.g., diurnal temperature range, DTR) or inter-day (e.g., difference of mean temperatures between neighbouring days) TV (Lee et al., 2018; Vicedo-Cabrera et al., 2016). However, these

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TV indicators may not fully capture the magnitude of recent temperature variations, because temperature change is a continuous process.

A novel and validated approach has been developed to assess the mortality effect of TV by combining intra- and inter-day temperature variations (Guo et al., 2016). Based on this new index, it has been estimated that 10 deaths per 100,000 population each year in Australia (1.7% of annual deaths) are attributable to TV exposure (Cheng et al., 2017). However, the actual disease burden associated with TV is likely to be much larger if the adverse effect on morbidity could be quantified. Hospitalizations have been used previously as a proxy measure for quantifying the non-fatal health burden associated with TV (mainly focusing on intra-day TV) but there are limited investigations on the relationship between TV with cause-specific outcomes. Moreover, there has been a marked decline in the disease burden related to extreme temperatures since the twentieth century, implying an evolved thermal adaptation in humans (Ha and Kim, 2013; Nordio et al., 2015; Vicedo-Cabrera et al., 2018). However, few studies have examined whether the strength of the association between TV and health outcomes has changed over time (Lee et al., 2018).

Most previous studies, conducted mainly in North America, Europe and Asia, have shown spatial heterogeneity in the relationship between TV and health outcomes (Gasparrini et al., 2015; Lee et al., 2018). By comparison, there are sparse data from South America, particularly from Brazil which covers nearly half the land mass of South America (Brazilian Institute of Geography and Statistics, 2016; Central Intelligence Agency, 2017). Brazil's wide range of climatic conditions and topographical types, as well as its unique location, suggest a varying distribution of TV and associated health outcomes (Alvares et al., 2013).

In this study, we use a national dataset to quantify the spatial and demographic variation in the association between TV and cause-specific hospitalizations in Brazil during 2000–2015. Further, by examining the temporal trend in the TV effect we will be able to determine to what extent humans have developed an adaptive capacity to variations in temperature.

2. Material and methods

2.1. Study area

Brazil is comprised of 26 states and one federal district with a total of 5570 cities. The country is subdivided into five regions according to geographic and socioeconomic differences: the north, northeast, southeast, south and central west (Brazilian Institute of Geography and Statistics, 2017).

2.2. Data sources

Between 1 January 2000 and 31 December 2015, data on daily hospitalizations in each city were collected through the Brazilian Unified Health System. The hospitalization records of some cities in early years were incomplete in the system, particularly for those in Northern Brazil. To examine the temporal change, 1814 cities with 16-year complete data, comprising 78.4% of the Brazilian population, contributed to the analysis. Fig. 1 shows the locations of each city and the population density of each region. Variables included patients' age, sex, date of admission, primary diagnosis [coded using the 10th version of the International Classification of Diseases (ICD-10)] and city of residence.

Daily data on weather conditions were extracted from a $0.25^{\circ} \times 0.25^{\circ}$ dataset that was interpolated using an inverse distance weighting method with data from 735 nationwide weather stations (Xavier et al., 2016). City-specific minimum and maximum temperatures ($Temp_{min}$ and $Temp_{max}$) were extracted from the grid overlaying the centre of each city. We followed the recommendation of the World Meteorological Organization (WMO, 2010) to define daily mean temperature ($Temp_{mean}$) as the mean value of the daily $Temp_{min}$ and $Temp_{max}$ due to the lack of data on actual $Temp_{mean}$.

Data on city-specific population were downloaded from the Brazilian Census 2000 and 2010 datasets (http://www.ibge.gov.br/censo/; http://www.censo2010.ibge.gov.br/). Data on standard population were collected from the World Standard Population Distribution (2000–2025) (Ahmad et al., 2001).

2.3. Data analysis

2.3.1. Definition of TV

In this study, TV was defined as the standard deviation (SD) of daily $Temp_{min}$ and $Temp_{max}$ during exposure days in order to properly capture the cumulative effect of both intra- and inter-day temperature fluctuations (Guo et al., 2016). For example, TV exposure for the current day and the preceding day one (TV0–1) was calculated as the SD ($Temp_{min_lag0}$, $Temp_{max_lag0}$, $Temp_{min_lag1}$, $Temp_{max_lag1}$).

2.3.2. Association between TV and hospitalizations

The association between TV and hospitalizations was quantified using a two-stage approach (Gasparrini et al., 2015; Guo et al., 2017; Hu et al., 2019). In the first stage, a quasi-Poisson regression model was performed on time-series data to obtain city-specific estimates of TV effect:

$$Y_{it} \sim poisson\ (\mu_{it});$$

$$Log\ (\mu_{it}) = \alpha + \beta TV_{it} + ns(\mathrm{Time}, 7\times\mathrm{year}) + cb(Temp_{mean}) + \gamma DOW_{it} + \delta Holiday_{it}$$

where Y_{it} is the daily number of hospitalizations in city i on day t; α is the intercept; TV_{it} is the linear function of TV because both previous studies and our initial analysis (see Fig. S1) have indicated that the relationships between TV and health outcomes are linear (Guo et al., 2016; Zhang et al., 2017); $ns(\mathrm{Time}, 7 \times \mathrm{year})$ is the natural cubic spline for time to control for the long-term trend and seasonality using 7 degrees of freedom (dfs) per year (Gasparrini et al., 2015); $cb(Temp_{mean})$ is the cross-basis function to estimate the nonlinear effect of $Temp_{mean}$ for up to lag 21 days, which could be an important confounder for assessing the TV effect (Gasparrini et al., 2015; Guo et al., 2014); natural cubic splines with 4 dfs are used for the mean temperature and the lags, respectively; DOW_{it} is a categorical variable for day of the week; $Holiday_{it}$ is a binary variable to control for public holidays.

We performed seven independent analyses by changing TV from the neighbouring two days (TV0–1) to eight days (TV0–7) to determine which exposure days were associated with the highest risk of hospitalization. The initial analysis indicated that the effect estimates associated with per 1 °C increase in TV were more heterogeneous than the results per interquartile range (IQR) increase in TV due to different ranges of city-specific TVs. Finally, the TV-hospitalization relationship was described as the percentage change in risk of hospitalization per IQR increase in TV [with 95% confidence interval (CI)].

In the second stage, the estimates of city-specific TV effect were pooled at the national and regional level using a random-effect meta-analysis with maximum likelihood estimation. Stratified analyses were performed by sex and 10 age-groups (i.e., 0–4, 5–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years). The various associations between TV and hospitalizations for 11 cause categories were also explored (classification of cause categories, see Table S1).

Sensitivity analyses were performed to check the robustness of the effect estimates by changing the maximum lag from 21 to 28 days and by changing the dfs for $Temp_{mean}$ from four to six. The confounding effect of relative humidity was evaluated using data from 265 weather stations provided by the Brazilian National Institute of Meteorology.

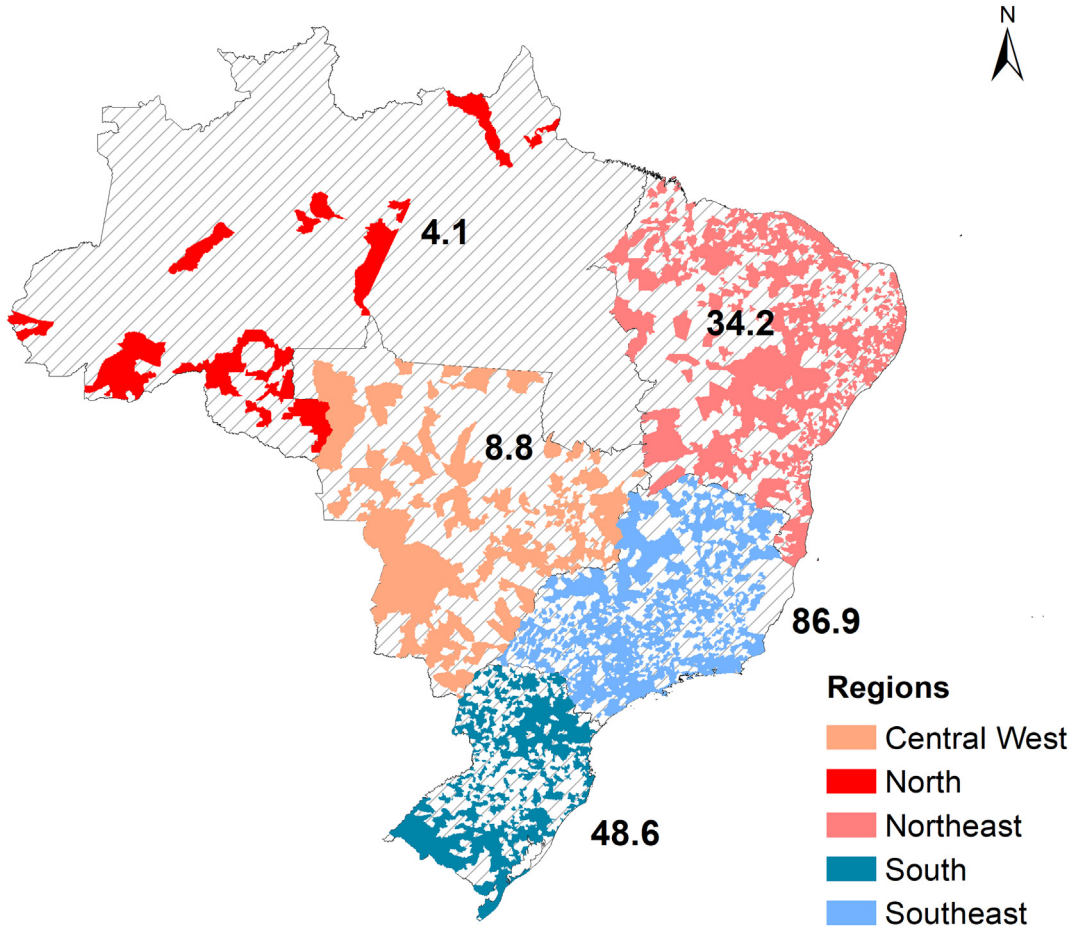

Fig. 1. The locations of 1814 cities and population densities (population per square kilometre) of the five Brazilian regions. Data on population density are extracted from the Brazilian Census 2010 dataset (http://www.censo2010.ibge.gov.br/).

2.3.3. Attributable hospitalizations

The daily attributable hospitalizations in each city (DAN_{it}) were calculated using the following equation (Gasparrini et al., 2012b):

$$DAN_{it} = Y_{it} \times \frac{RR_{it} - 1}{RR_{it}};$$

$$RR_{it} = EXP\left(\frac{\beta}{IQR_i} \times TV_{it}\right)$$

where Y_{it} is the daily number of hospitalizations in city i on day t; RR_{it} is the relative risk (RR) of hospitalization associated with TV exposure during the current day and preceding few days; β is the risk coefficient per IQR increase in TV at city i. In this study, city-specific β was replaced using the pooled risk coefficient at regional level because some small cities had limited patients, which led to the abnormal TV-hospitalization relationship.

The total number of attributable hospitalizations in each city (AN_{it}) was calculated by summing up DAN_{it}; attributable fraction and attributable rate of hospitalizations (per 100,000 population) at the national and regional level were calculated by dividing AN_{it} by the number of hospitalizations and population, respectively. Considering the grouping limitation of the Brazilian Census 2000 and 2010 datasets, we merged the population aged ≥ 60 years when calculating the attributable rate of hospitalizations.

2.3.4. Long-term change in TV effect

We examined the long-term change in the effect of TV using a two-stage strategy: first, the city-year-specific association between TV and hospitalizations was estimated using the above mentioned quasi-Poison regression model. Second, a meta-regression model was performed at the national and regional level, with setting the predictor (i.e., year) as independent variable and city-year-specific estimates as the dependent variable.

All data analyses were performed using R software (version 3.4.1). The "dlnm" package was used to fit the nonlinear lagged effect of daily mean temperature (Gasparrini et al., 2010); The "mvmeta" was used for the second-stage meta-analysis and the meta-regression (Gasparrini et al., 2012a, b; Viechtbauer, 2010). Cochran Q test and I^2 statistic were applied to assess the residual heterogeneity for meta-analysis and meta-regression. Statistical tests were two-sided with p values < 0.05 treated as statistically significant.

3. Results

There were 147,959,243 (59% female) hospitalizations collected from 1814 cities during 2000–2015, with 66% of cases aged 10–59 years (Table 1 and Table S2). The age-standardised rate (ASR) of hospitalizations was 6.4% per year at the national level, varying from 5.8% in the southeast to 7.2% in the central west. The daily mean temperature of each city ranged between 15.7 and 28.8 °C. The city-specific TV declined from 3.6–8.7 °C on 0–1 days to 3.3–7.9 °C on 0–7 days.

3.1. Association between TV and hospitalizations

At the national level, the estimate of TV effect was strongest on 0–1 days' exposure: per IQR increase in TV was associated with 1.07% [95%CI: 1.02–1.12%] increase in the risk of hospitalization (Fig. 2).

Table 1
Summary of hospitalizations and city-specific temperature characteristics (with standard deviation) by region during 2000–2015.

	No. cities	Pop (%)	Cases	Annual rate of hospitalizations (%)		City-specific (°C)		
				Crude	Age-standardised	Mean temp	TV0–1	TV0–7
National	1814	78.4	147,959,243	6.4	6.4	23.5 ± 2.8	6.2 ± 0.8	5.8 ± 0.8
Region								
North	28	26.3	3,904,208	6.2	6.4	27.1 ± 0.7	5.8 ± 0.6	5.3 ± 0.6
Northeast	662	78.0	42,875,430	6.7	6.7	26.0 ± 1.6	5.7 ± 0.9	5.2 ± 0.8
Central West	128	80.7	11,997,508	6.9	7.2	25.0 ± 1.3	7.0 ± 0.3	6.5 ± 0.3
Southeast	622	87.0	63,859,654	5.9	5.8	22.3 ± 1.5	6.6 ± 0.6	6.2 ± 0.5
South	374	83.2	25,322,443	7.1	7.1	20.2 ± 1.5	6.1 ± 0.5	5.9 ± 0.5

Note: Pop, population coverage; temp, daily temperature; TV, temperature variability.

The strength of effect estimates decreased with time and plateaued after TV0–4. Regionally, the estimate of TV effect was highest in the central west and lowest in the north and south. The I^2 value of meta-analysis at TV0–1 was 16.4% at the national level, ranging substantially from 0.0% in the north to 25.8% in the central west.

3.2. Age and sex-specific effect estimates of TV

Fig. 3 compares the sex-specific age difference in TV effect on 0–1 days' exposure (age-specific results for both sex, males, and females see Figs. S2–S4). The estimate of TV0–1 effect was higher in males [1.32% (95%CI: 1.25–1.39%)] than in females [0.88% (95%CI: 0.82–0.93%)]. When examined by age-group, there was a reverse J-shape such that the association was strongest in children – particularly those aged under five years - and the elderly. There was no substantial difference in the estimate of TV0–1 effect between males and females for most age-groups, except that males 10–49 year old were more affected than females.

3.3. Cause-specific effect estimates of TV

There was a marked variation in the size of TV effect on different hospitalization causes (Fig. 4): the strongest effect occurred with respiratory admissions on 0–7 days' exposure whereas the TV effect declined to be negative for cardiovascular admissions if longer than 0–4 days' exposure. The effect of TV peaked on 0–1 days' exposure for all causes of hospitalizations with the exception of certain infectious and parasitic diseases, respiratory diseases, and perinatal conditions. Figs. S5–S6 show the lag patterns of the effect estimates of temperature variability for 11 cause categories. Cardiovascular admissions had the strongest harvesting effect.

3.4. Attributable burden of hospitalizations due to TV

During 2000–2015, 5,141,816 (95%CI: 4,646,015–5,635,099) of nationwide hospitalizations, accounting for 3.5% (95%CI: 3.1–3.8%) of cases, could be attributable to TV0–1 exposure (Table 2). This equated to an annual rate (crude) of 221 (95%CI: 200–242) hospitalizations per 100,000 population. The attributable rate for the under-fives was 5–8 times higher than in adults aged 20–49 years and twice as high in those aged ≥ 60 years. The attributable ASRs were similar between males and females. However, sex difference existed across age-groups (see Tables S3–S4): females aged 20–29 years had a higher attributable ASR than males.

Regionally, the attributable rate of hospitalizations in the central west was highest − nearly twice as high than in the south and north. The attributable fraction, and rate of hospitalizations for each city are shown in Fig. S7. City-specific attributable rates ranged from 53 to 874 cases per 100,000 population, with the majority of the most affected cities located in the central west and the inland of northeast.

3.5. Long-term trend in the effect estimate of TV

Fig. 5 shows the annual change in the coefficient of TV0–1 effect at the national and regional level. From 2000 to 2015, the estimate of TV0–1 effect increased at the national level, and in the north and southeast. In contrast, there was no significant change in TV0–1 effect in other three regions.

Sensitivity analyses indicated that the estimates of TV effect were robust after changing the maximum lag from 21 to 28 days, the dfs from four to six for $Temp_{mean}$, and including relative humidity in the models (see Figs. S8–S10).

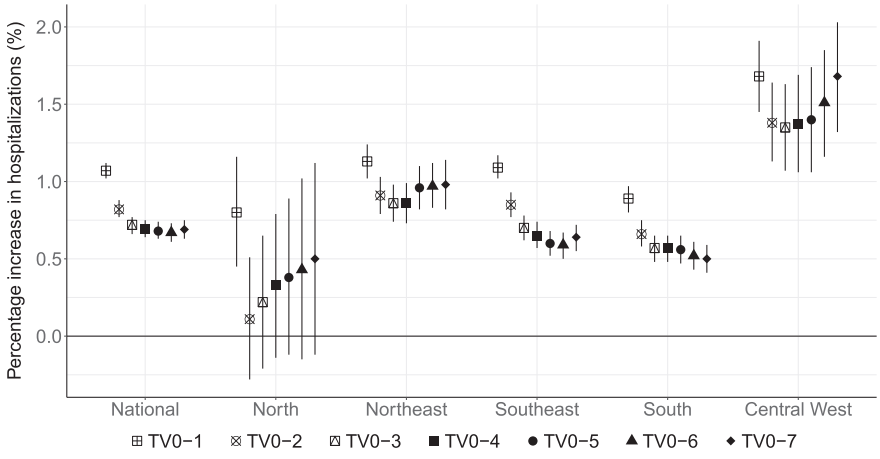

Fig. 2. Effect estimates of temperature variability (TV, per interquartile range increase) from 0–1 days' to 0–7 days' exposure at the national and regional level.

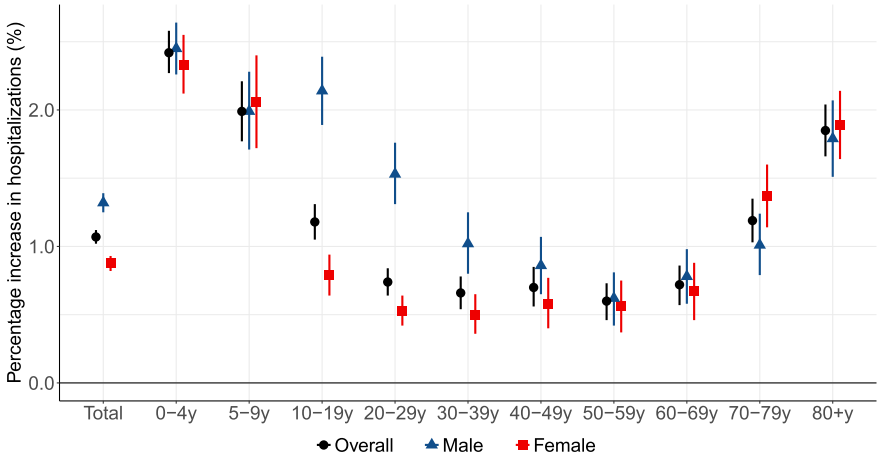

Fig. 3. Age-specific effect estimates of temperature variability (TV, per interquartile range increase) on 0–1 days' exposure by sex. Age-specific results from 0–1 days' to 0–7 days' exposure are provided in Figs. S2–S4.

4. Discussion

This is the first study to comprehensively quantify the relationship between TV and hospitalizations of all-cause and cause-specific over time. Consistent with mortality evidence derived from other continents (Cheng et al., 2017; Zhang et al., 2017), TV has a significant and independent impact on healthcare utilisation in the Brazilian population: for every IQR increase in TV0–1, the risk of hospitalization rose by 1.07%. This is a stronger association than what has previously been reported in this population between TV and mortality using a comparable approach (Guo et al., 2016). Assuming a causal association, more than five million hospitalizations could be attributed to TV on 0–1 days' exposure between 2000 and 2015.

The physiological mechanisms that have been posited to explain the relationship between TV and adverse health outcomes in humans remain uncertain. Inadequate thermoregulatory control and its adverse effects on the cardiovascular and immune systems for example, may contribute to the excess morbidity and mortality associated with TV (Ding et al., 2016; Graudenz et al., 2006; Wang et al., 2013). In addition, some personal behaviours are mainly determined by the forecasted daily mean temperature, which may not protect individuals from TV exposure. For example, a hot day with a sudden drop in temperatures might result in many people being caught outside or having to return home without enough clothes that could protect them from the cold.

The effect of TV on hospitalizations varied not only by duration of exposure to TV, but also by cause of admission, sex and age-group, and region of the country. The estimate of TV effect was most pronounced (with the exception of a couple of cause-specific outcomes) on 0–1 days' exposure in Brazil. Although consistent with findings from studies of relatively hot countries (e.g. Thailand), our results differed to those from countries where longer exposure to TV appeared to be more detrimental such as Australia, Spain and the United States (Cheng et al., 2017; Guo et al., 2016). We speculate that the more acute effect of TV among populations from hot countries may be associated with local climatic adaptation and modified by a variety of country-specific characteristics related to behaviour and technology (Guo et al., 2016).

In this study, we observed TV to be most strongly associated with respiratory admissions, especially during long exposure days. In contrast, the association between TV and cardiovascular admissions declined possibly due to a strong harvesting effect. Similar findings were reported by studies in China and Korea of the DTR-morbidity relationship for the two diseases (Lim et al., 2012a; Wang et al., 2013). However, a TV-mortality study in Hubei, China during 2009–2012 reported lag patterns of the two fatal outcomes completely opposite to ours (Zhang et al., 2017). Another study in the United States also reported a higher risk of cardiovascular death associated with DTR than for respiratory death (Lim et al., 2015). Despite different study designs and populations, these opposing findings possibly imply a hypothesis: the inverse relationship between cardiovascular admissions and TV

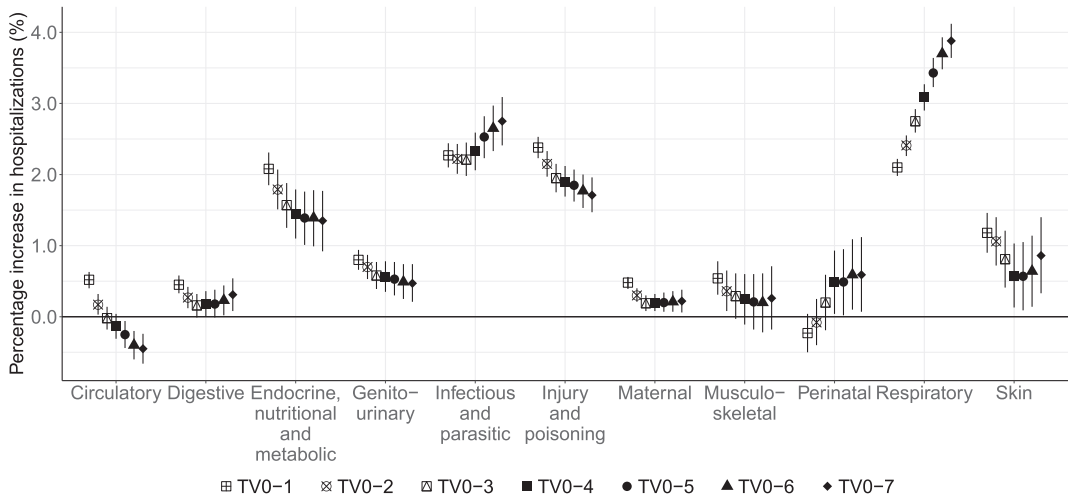

Fig. 4. Cause-specific effect estimates of temperature variability (TV, per interquartile range increase) from 0–1 days' to 0–7 days' exposure.

Table 2
Hospitalizations (with 95% confidence intervals) attributable to temperature variability on 0–1 days' exposure in the 1814 enrolled cities during 2000–2015.

	Attributable cases	Attributable fraction (%)	Annul attributable rate (per 100,000 population)	
			Crude	Age-standardised
National	5,141,816 (4,646,015, 5,635,099)	3.5 (3.1, 3.8)	221 (200, 242)	224 (170, 277)
Region				
North	113,504 (63,707, 162,609)	2.9 (1.6, 4.2)	179 (101, 257)	194 (−89, 462)
Northeast	1,783,754 (1,610,734, 1,955,994)	4.2 (3.8, 4.6)	277 (250, 303)	273 (208, 337)
Central West	591,430 (512,829, 669,455)	4.9 (4.3, 5.6)	341 (296, 386)	345 (232, 456)
Southeast	2,029,367 (1,893,006, 2,165,405)	3.2 (3.0, 3.4)	186 (174, 199)	184 (153, 215)
South	623,761 (565,739, 681,636)	2.5 (2.2, 2.7)	175 (159, 192)	180 (137, 222)
Sex				
Male	2,543,408 (2,252,530, 2,831,963)	4.2 (3.7, 4.7)	221 (196, 247)	230 (159, 298)
Female	2,554,792 (2,208,516, 2,898,836)	2.9 (2.5, 3.3)	217 (187, 246)	218 (143, 293)
Age (years)				
0–4	1,351,790 (1,186,307, 1,514,147)	7.9 (7.0, 8.9)	773 (679, 866)	–
5–9	338,892 (268,133, 407,945)	6.5 (5.1, 7.8)	183 (145, 220)	–
10–19	580,803 (456,279, 703,538)	3.8 (3.0, 4.6)	138 (109, 168)	–
20–29	671,620 (494,855, 846,615)	2.3 (1.7, 3.0)	159 (117, 201)	–
30–39	421,015 (274,168, 566,127)	2.1 (1.4, 2.8)	115 (75, 155)	–
40–49	306,196 (168,086, 442,251)	1.9 (1.1, 2.8)	101 (56, 147)	–
50–59	266,439 (145,116, 386,140)	1.8 (1.0, 2.7)	122 (67, 177)	–
60–69	276,191 (172,422, 378,472)	2.3 (1.4, 3.2)	404 (291, 516)	–
70–79	347,205 (251,643, 441,162)	3.5 (2.5, 4.4)		
≥80	350,735 (277,320, 422,778)	5.2 (4.1, 6.3)		

exposure may be contributed by depletion of susceptible individuals due to high cardiovascular mortality. To test this, further studies are needed to explore cause-specific mortality associated with TV exposure in Brazil.

In our study, we observed an enhanced vulnerability to TV in children and the elderly, potentially because of physiological inability to respond adequately to the unstable weather in these individuals (Chan et al., 2010; Chen et al., 2011; Fleg and Strait, 2012; González-Alonso, 2012). This age pattern of TV effect continued for the attributable rate of hospitalizations. Indeed, our analysis indicates that the attributable hospitalization burden for children aged under 5 years were twice as high as in the elderly. This is in line with previous findings that nearly 90% of the disease burden related to climate change (e.g., temperature anomalies) occurs in the under-fives, particularly in low- and middle-income countries like Brazil (Haines et al., 2006; Ying Zhang MBBS, 2007). The greater vulnerability to TV exposure in the under-fives may be explained by children's higher exposure per unit of weight and their having a weaker adaptive capacity than typically present in adults (Landrigan and Garg, 2005; Medicine and Fitness, 2000).

Previous studies have suggested that females may be more associated with the effect of TV (Lim et al., 2012b; Yang et al., 2013; Zhou et al., 2014). Inconsistently, our finding indicates that in Brazil men 10–49 year old may be more affected by exposure to TV than women, while there is non-significant sex difference for the TV effect across other age-groups. This may be explained by higher levels of outdoor activities (e.g., football), and thus greater exposure to TV, among young and middle-aged men. However, the rate of attributable hospitalization was equally distributed between men and women in Brazil, after adjusting for population size and age structure. Despite this, a higher attributable burden was observed for women of childbearing age, which may be contributed by the high number of hospitalizations for maternal conditions – the association of which with TV has been reported in other countries (Auger et al., 2015; Molina and Saldarriaga, 2017).

Some investigations have also suggested that the effect of TV on health outcomes exhibits regional disparity within a country, possibly due to local climactic and socioeconomic factors (Gasparrini et al., 2015; Guo et al., 2014; Laaidi et al., 2006). However, difference in population structure (i.e., age and sex) precludes the direct comparison between these studies, particularly for findings derived from countries with high population migration. After adjustments by age and sex, we observed that in Brazil the attributable burden of TV was highest in the central west, where the local climate is characterized as moderate but with greater fluctuations in temperature, relative to other regions (Alvares et al., 2013). Compared with the cold and hot areas of the country, living in more temperate areas of Brazil may result in less use of artificial methods for temperature control (e.g., air conditioning and building insulation) as well as greater time spent outdoors, which increases the level of exposure to TV. In addition, the prevalent occupations in the central west, namely farming and livestock breeding, may further exacerbate TV-related hospitalizations due to longer period of time spent outdoors relative to other occupations (The Brazil Business, 2013).

Nationally, the strength of the association between TV and risk of hospitalization in Brazil has increased from 2000 to 2015. A recent multi-country study exploring the effect of DTR on mortality observed a similar long-term rise in Brazil and other few countries, explaining it as partly due to a synergistic effect between the warmer daily temperature and aged population (Lee et al., 2018). However, the regional variation in the changing nature of TV effect implies that the underlining reasons may go deeper because all the five areas have been experiencing global warming and population aging (Brazilian Institute of Geography and Statistics, 2013; Xavier et al., 2016). More research is thus needed to clarify the underpinning mechanisms. Overall, there was no evidence from this study to suggest that there has been human adaptation to TV exposure (although a decline trend was found in the central west, the reduction was still statistically non-significant). If so, then the effect of TV on population health in the future may not diminish, especially when considering that TV is projected to increase for most of the Brazilian territory over coming decades (Lindvall and Svensson, 2015).

This study has several limitations. We calculated TV using temperature data from a gridded dataset, which may have introduced measurement bias compared with the individual exposure data. However, this may result in an underestimation of the TV effect. The calculation of daily $Temp_{mean}$ was simplified as the average of daily $Temp_{min}$ and $Temp_{max}$ due to the lack of data on actual $Temp_{mean}$ (WMO, 2010). Although this simplification may bias the cofounding effect of daily $Temp_{mean}$, our main findings should not change substantially because of the very high correlation between actual $Temp_{mean}$ and average of daily $Temp_{min}$ and $Temp_{max}$. In this study, data on hospitalizations from 3756 out of 5570 cities were not available for inclusion. However, the 1814 cities that comprised our dataset cover

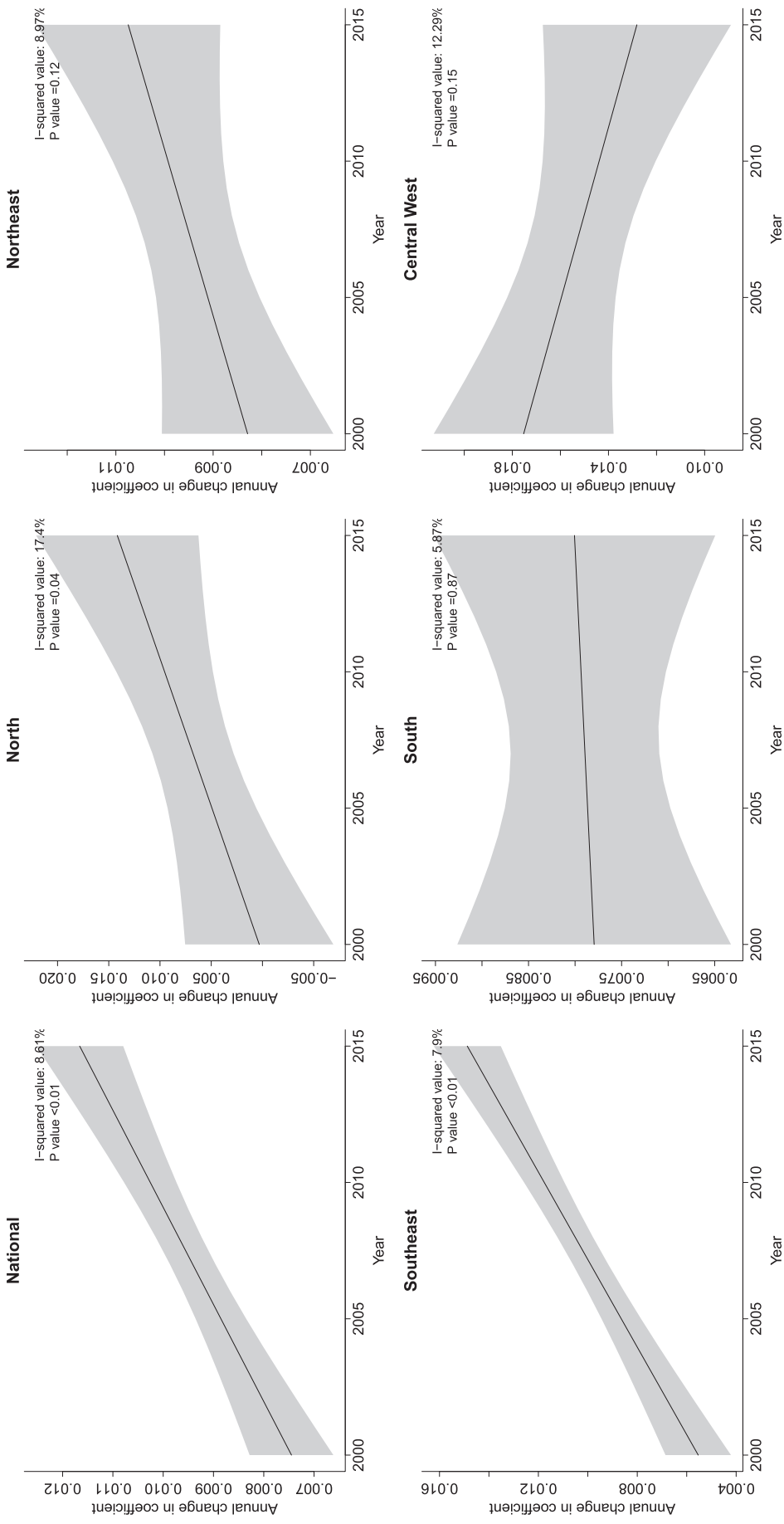

Fig. 5. The annual change in the risk coefficient of temperature variability (per interquartile range increase) on 0–1 days' exposure at the national and regional level.

four-fifths of the national population, supporting the representativeness of our findings. As with other studies (Lim et al., 2012a; Lin et al., 2009; O'Neill and Ebi, 2009; Sung et al., 2011), we analysed data on all hospitalizations due to the lack of necessary information to distinguish whether an admission was emergency or not, although this was the best dataset we could get in Brazil. As a result, the adverse effect of TV may be biased. We did not control for air pollutants in the main analyses due to the lack of monitoring data for most Brazilian cities. However, our findings are likely to be robust, as previous studies have indicated that the associations between temperature and health outcomes are largely unaffected by adjustment for air pollutants (Guo et al., 2014; Zhao et al., 2017).

5. Conclusions

Findings from this study indicate that TV is an independent predictor for hospitalizations from a variety of health-related conditions, but, in particular, from respiratory disease in the Brazilian population. Young children and, to a lesser extent, the elderly, are most susceptible to modest temperature fluctuations, possibly reflecting impaired thermoregulatory response relative to other age-groups. The difference in lag pattern compared with other countries indicates the specificity of TV-related health conditions in Brazil. Compared with extreme temperatures which are relatively infrequent events, the adverse impact of unstable weather is likely to be responsible for a greater burden of morbidity, particularly in lower- and middle-income countries.

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Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the paper.

Ethics committee approval

Ethical approval was not required for secondary analysis of aggregate anonymous data from the Brazilian Hospital Information System.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.08.021.

References

Ahmad, O.B., Boschi-Pinto, C., Lopez, A.D., Murray, C.J., Lozano, R., Inoue, M., 2001. Age Standardization of Rates: A New WHO Standard. 31. World Health Organization, Geneva, pp. 1–14.
Alvares, C.A., Stape, J.L., Sentelhas, P.C., de Moraes, G., Leonardo, J., Sparovek, G., 2013. Köppen's climate classification map for Brazil. Meteorol. Z. 22, 711–728.
Auger, N., Fraser, W.D., Smargiassi, A., Kosatsky, T., 2015. Ambient heat and sudden infant death: a case-crossover study spanning 30 years in Montreal, Canada. Environ. Health Perspect. 123, 712.
Brazilian Institute of Geography and Statistics, 2013. Population projection of Brazil by sex and age: 2000–2060 (Available). http://www.ibge.gov.br/english/estatistica/populacao/projecao_da_populacao/2013/default.shtm, Accessed date: 2 September 2017.
Brazilian Institute of Geography and Statistics, 2016. Brazilian territorial area (Available). http://www.ibge.gov.br/english/geociencias/cartografia/default_territ_area.shtm, Accessed date: 16 August 2017.
Brazilian Institute of Geography and Statistics, 2017. Division into regions (Available). http://www.ibge.gov.br/english/geociencias/geografia/default_div_int.shtm, Accessed date: 16 August 2017.
Central Intelligence Agency, 2017. The World fact book: South America - Brazil (Available). https://www.cia.gov/library/publications/the-world-factbook/wfbExt/region_soa.html, Accessed date: 16 August 2017.
Chan, S.L., Wei, Z., Chigurupati, S., Tu, W., 2010. Compromised respiratory adaptation and thermoregulation in aging and age-related diseases. Ageing Res. Rev. 9, 20–40.
Chen, C., WenHao, Z., YongHao, G., HaiDong, K., 2011. Diurnal temperature range as a novel risk factor for sudden infant death. Biomed. Environ. Sci. 24, 518–522.
Cheng, J., Xu, Z., Bambrick, H., Su, H., Tong, S., Hu, W., 2017. The mortality burden of hourly temperature variability in five capital cities, Australia: time-series and meta-regression analysis. Environ. Int. 109, 10–19.
Ding, Z., Li, L., Xin, L., Pi, F., Dong, W., Wen, Y., et al., 2016. High diurnal temperature range and mortality: effect modification by individual characteristics and mortality causes in a case-only analysis. Sci. Total Environ. 544, 627–634.
Fleg, J.L., Strait, J., 2012. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart Fail. Rev. 17, 545–554.
Gasparrini, A., Armstrong, B., Kenward, M., 2010. Distributed lag non-linear models. Stat. Med. 29, 2224–2234.
Gasparrini, A., Armstrong, B., Kenward, M., 2012a. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat. Med. 31, 3821–3839.
Gasparrini, A., Armstrong, B., Kovats, S., Wilkinson, P., 2012b. The effect of high temperatures on cause-specific mortality in England and Wales. Occup. Environ. Med. 69, 56–61.
Gasparrini, A., Guo, Y., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., et al., 2015. Mortality risk attributable to high and low ambient temperature: a multi-country observational study. Lancet 386, 369–375.
González-Alonso, J., 2012. Human thermoregulation and the cardiovascular system. Exp. Physiol. 97, 340–346.
Graudenz, G.S., Landgraf, R.G., Jancar, S., Tribess, A., Fonseca, S.G., Faé, K.C., et al., 2006. The role of allergic rhinitis in nasal responses to sudden temperature changes. J. Allergy Clin. Immunol. 118, 1126–1132.
Guo, Y., Gasparrini, A., Armstrong, B., Li, S., Tawatsupa, B., Tobias, A., et al., 2014. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. Epidemiology 25, 781.
Guo, Y., Gasparrini, A., Armstrong, B., Tawatsupa, B., Tobias, A., Lavigne, E., et al., 2016. Temperature variability and mortality: a multi-country study. Environ. Health Perspect. 124, 1554.
Guo, Y., Gasparrini, A., Armstrong, B., Tawatsupa, B., Tobias, A., Lavigne, E., et al., 2017. Heat wave and mortality: a multicountry, multicommunity study. Environ. Health Perspect. 125, 087006.
Ha, J., Kim, H., 2013. Changes in the association between summer temperature and mortality in Seoul, South Korea. Int. J. Biometeorol. 57, 535–544.
Haines, A., Kovats, R.S., Campbell-Lendrum, D., Corvalán, C., 2006. Climate change and human health: impacts, vulnerability and public health. Public Health 120, 585–596.
Hu, K., Guo, Y., Yang, X., Zhong, J., Fei, F., Chen, F., Zhao, Q., Zhang, Y., Chen, G., Chen, Q., Ye, T., 2019. Temperature variability and mortality in rural and urban areas in Zhejiang province, China: an application of a spatiotemporal index. Sci. Total Environ. 647, 1044–1045.
Intergovernmental Panel on Climate Change, 2015. Climate Change 2014: Mitigation of Climate Change. Cambridge University Press.
Laaidi, M., Laaidi, K., Besancenot, J.-P., 2006. Temperature-related mortality in France, a comparison between regions with different climates from the perspective of global warming. Int. J. Biometeorol. 51, 145–153.
Landrigan, P., Garg, A., 2005. In: Pronczuk-Garbino, J. (Ed.), Children are not Little Adults. Children's Health and the Environment—A Global Perspective: A Resource Manual for the Health Sector. World Health Organization, Geneva, pp. 3–16.
Lee, W., Bell, M.L., Gasparrini, A., Armstrong, B.G., Sera, F., Hwang, S., et al., 2018. Mortality burden of diurnal temperature range and its temporal changes: a multi-country study. Environ. Int. 110, 123–130.
Lim, Y.-H., Hong, Y.-C., Kim, H., 2012a. Effects of diurnal temperature range on cardiovascular and respiratory hospital admissions in Korea. Sci. Total Environ. 417, 55–60.
Lim, Y.-H., Park, A.K., Kim, H., 2012b. Modifiers of diurnal temperature range and mortality association in six Korean cities. Int. J. Biometeorol. 56, 33–42.
Lim, Y.-H., Reid, C.E., Mann, J.K., Jerrett, M., Kim, H., 2015. Diurnal temperature range and short-term mortality in large US communities. Int. J. Biometeorol. 59,

1311–1319.
Lin, S., Luo, M., Walker, R.J., Liu, X., Hwang, S.-A., Chinery, R., 2009. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. Epidemiology 738–746.
Lindvall, J., Svensson, G., 2015. The diurnal temperature range in the CMIP5 models. Clim. Dyn. 44, 405–421.
Medicine, CoS, Fitness, 2000. Climatic heat stress and the exercising child and adolescent. Pediatrics 106, 158–159.
Molina, O., Saldarriaga, V., 2017. The perils of climate change: in utero exposure to temperature variability and birth outcomes in the Andean region. Econ. Hum. Biol. 24, 111–124.
Nordio, F., Zanobetti, A., Colicino, E., Kloog, I., Schwartz, J., 2015. Changing patterns of the temperature–mortality association by time and location in the US, and implications for climate change. Environ. Int. 81, 80–86.
O'Neill, M.S., Ebi, K.L., 2009. Temperature extremes and health: impacts of climate variability and change in the United States. J. Occup. Environ. Med. 51, 13–25.
Sung, T.-I., Chen, M.-J., Lin, C.-Y., Lung, S.-C., Su, H.-J., 2011. Relationship between mean daily ambient temperature range and hospital admissions for schizophrenia: results from a national cohort of psychiatric inpatients. Sci. Total Environ. 410, 41–46.
The Brazil Business, 2013. Brazilian regions (Available). http://thebrazilbusiness.com/article/brazilian-regions, Accessed date: 23 November 2017.
Vicedo-Cabrera, A.M., Forsberg, B., Tobias, A., Zanobetti, A., Schwartz, J., Armstrong, B., et al., 2016. Associations of inter-and intraday temperature change with mortality. Am. J. Epidemiol. 183, 286–293.
Vicedo-Cabrera, A.M., Sera, F., Guo, Y., Chung, Y., Arbuthnott, K., Tong, S., et al., 2018. A multi-country analysis on potential adaptive mechanisms to cold and heat in a changing climate. Environ. Int. 111, 239–246.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 1–48.
Wang, M.-z., Zheng, S., He, S.-l., Li, B., Teng, H.-J., Wang, S.-g., et al., 2013. The association between diurnal temperature range and emergency room admissions for cardiovascular, respiratory, digestive and genitourinary disease among the elderly: a time series study. Sci. Total Environ. 456, 370–375.
WMO, 2010. Guide to Climatological Practices WMO-No. 100, 3rd edn. World Meteorological Organization, Geneva.
Xavier, A.C., King, C.W., Scanlon, B.R., 2016. Daily gridded meteorological variables in Brazil (1980–2013). Int. J. Climatol. 36, 2644–2659.
Yang, J., Liu, H.-Z., Ou, C.-Q., Lin, G.-Z., Zhou, Q., Shen, G.-C., et al., 2013. Global climate change: impact of diurnal temperature range on mortality in Guangzhou, China. Environ. Pollut. 175, 131–136.
Ying Zhang MBBS, M., 2007. Climate change and disability-adjusted life years. J. Environ. Health 70, 32.
Zhang, Y., Yu, C., Bao, J., Li, X., 2017. Impact of temperature variation on mortality: an observational study from 12 counties across Hubei Province in China. Sci. Total Environ. 587, 196–203.
Zhao, Q., Zhang, Y., Zhang, W., Li, S., Chen, G., Wu, Y., et al., 2017. Ambient temperature and emergency department visits: time-series analysis in 12 Chinese cities. Environ. Pollut. 224, 310–316.
Zhou, X., Zhao, A., Meng, X., Chen, R., Kuang, X., Duan, X., et al., 2014. Acute effects of diurnal temperature range on mortality in 8 Chinese cities. Sci. Total Environ. 493, 92–97.